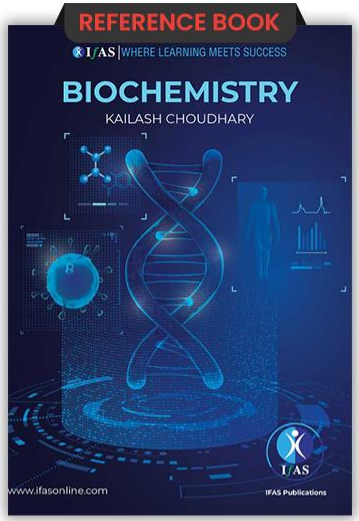
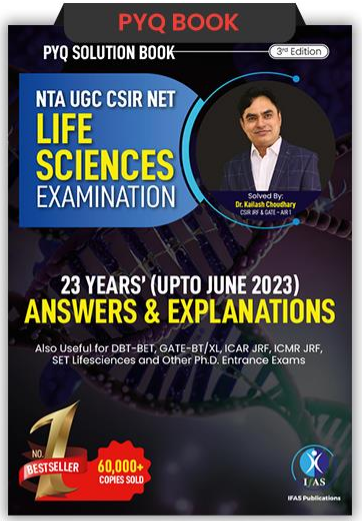
"Success is the sum of small efforts - repeated day in and day out"

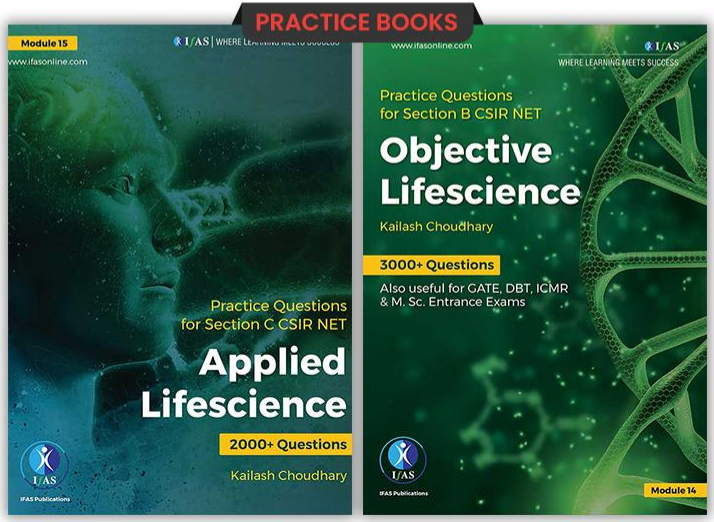
CSIR NET – Life Science

Unit 1: Biochemistry

15 Lipid and Amino Acid Metabolism







IfAS

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Points to be covered in this Lecture

- Fatty Acid Oxidation
- Fatty Acid Biosynthesis
- Cholesterol Biosynthesis
- Amino Acid Metabolism
- Urea Cycle
- Purine Nucleotude Biosynthesis
- Purine Nucleotide Catabolism

Lipid Metabolism

Triacylglycerols (TAG) are the most predominant storage form of energy.

- Adipose Tissues
- Liver

Two main benefits for fat being the energy reserve

- **Highly reduced** → Yield more energy — 9 K.cal/g
- **Non-polar and hydrophobic** → occupy lesser space

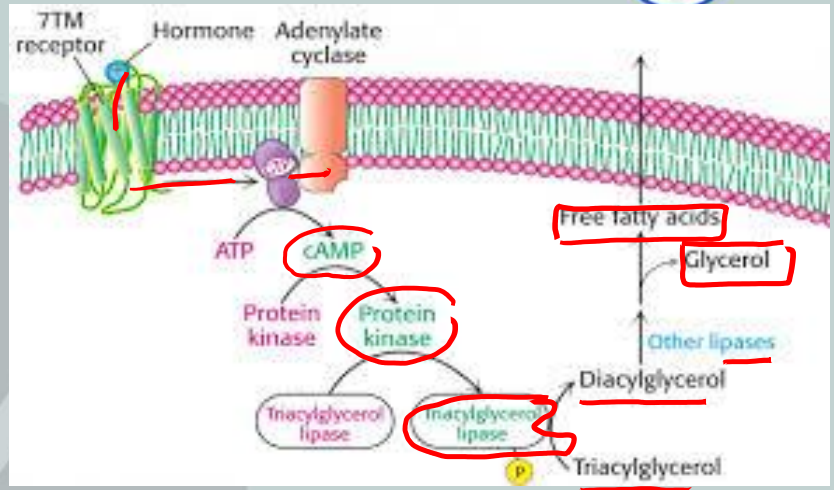
Lipid Oxidation : Aerobic condition

TAG —Lipase→ Glycerol + 3FA

Regulation of Hormone Sensitive Lipase

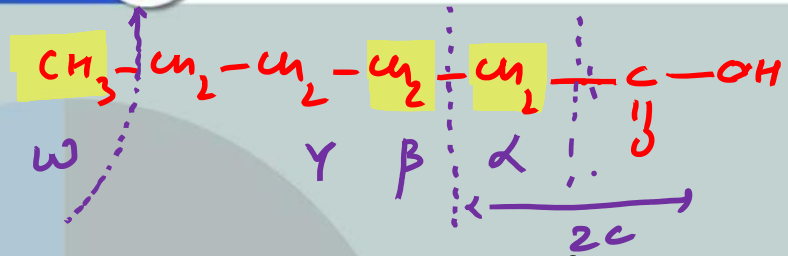
- Blood Glucose – Low
- Glucagon – High
- Glucagon Signalling leads to Phosphorylation of TAG Lipase
- Lipase Enzyme becomes active
- TAG is converted into free fatty acid and Glycerol

DAG → MAG → Glycerol
DAG —FA→ MAG —FA→ Glycerol



Glycerol ⇅ DHAP → Glucose

Fatty Acid Oxidation:



Alpha oxidation (α-oxidation):

Branched chain fatty acids (Phytanic acid) are broken down by removal of a single carbon from the carboxyl end.

Location: Peroxisome

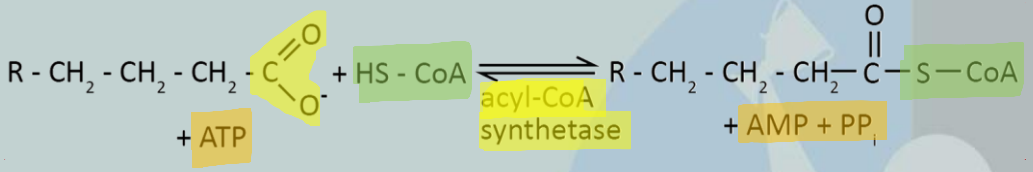
Omega Oxidation:

Alternative oxidation pathway for β-oxidation when β-oxidation is blocked.

Location: The smooth ER of liver and kidney cells

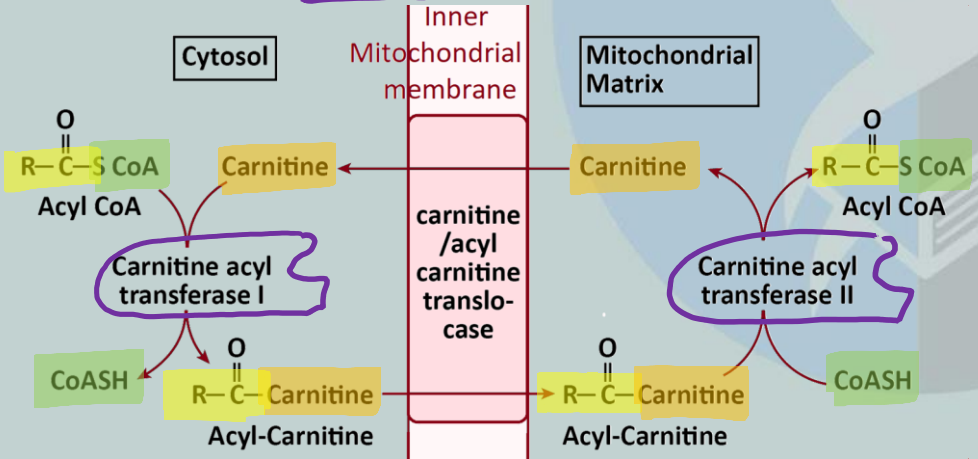
Beta Oxidation: Major oxidation. Mitochondria (Animals), Peroxisome (Plants)

1. Fatty Acid Activation:



- Acyl CoA Synthetase (Thio Kinase)
- 2ATP equivalent energy

2. Transport of Acyl CoA into mitochondria : in form of Acyl carnitine



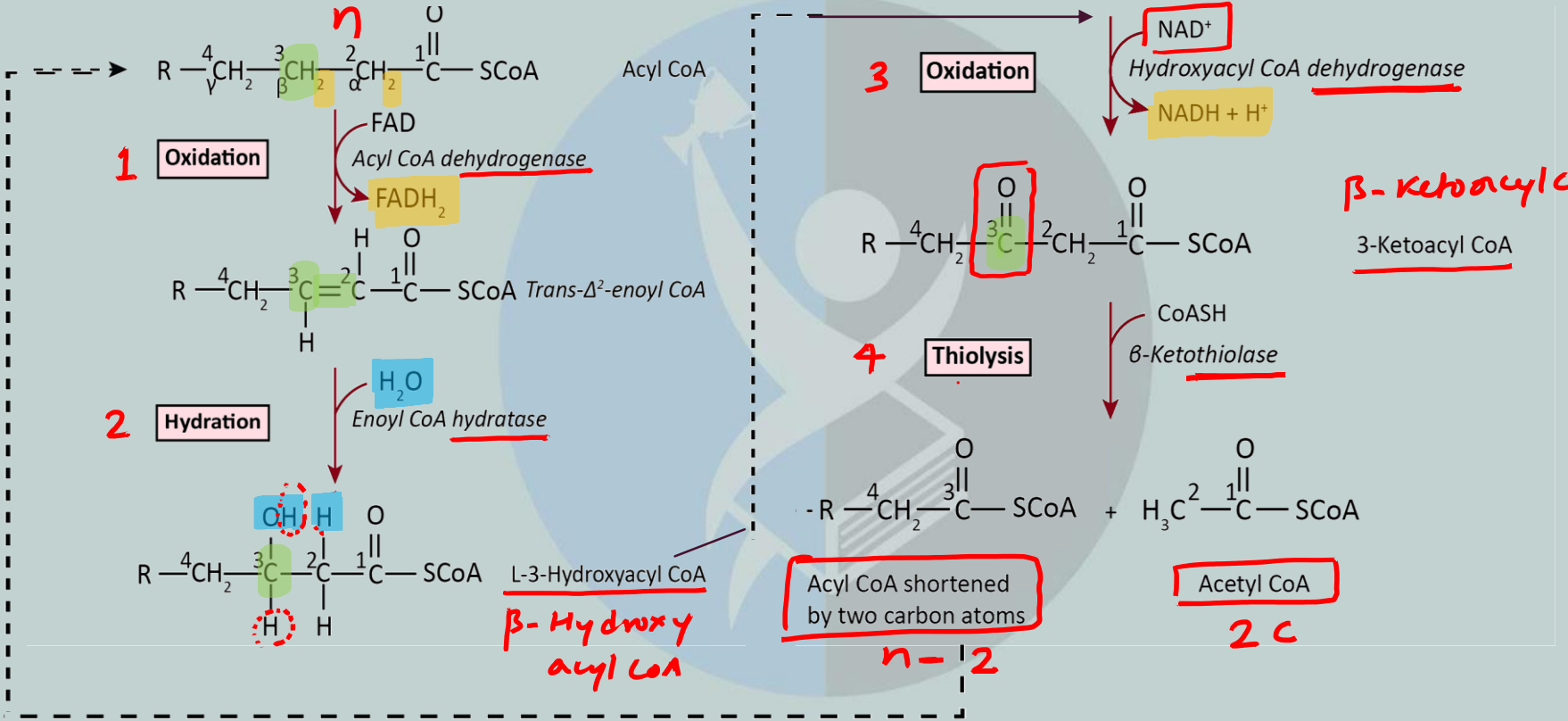
Regulatory enzyme

CAT-I

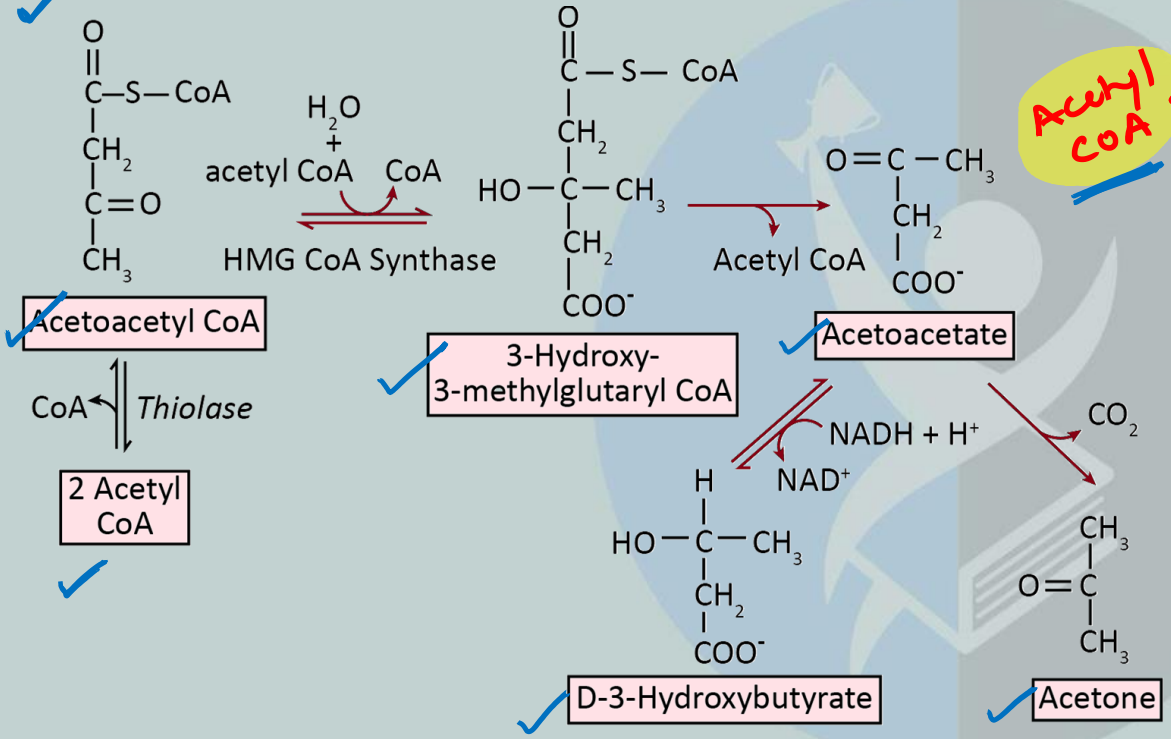
⊖

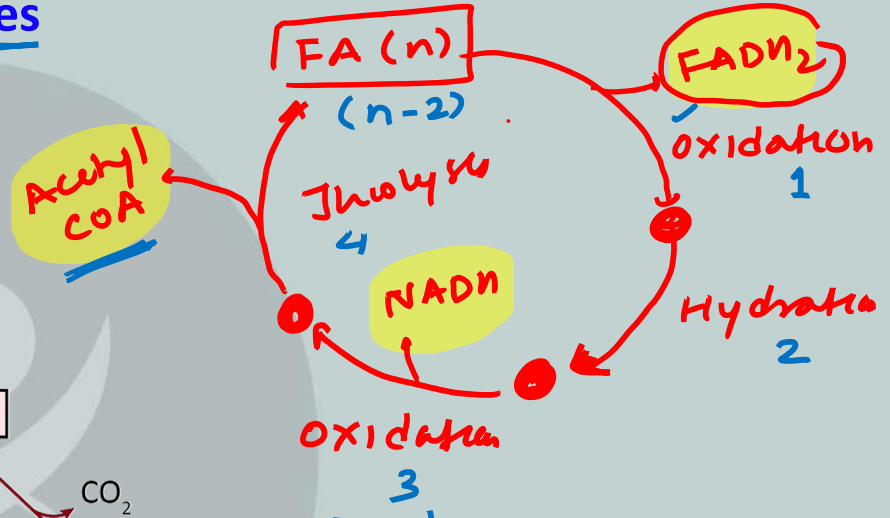
Malonyl CoA (Biosynthesis of FA)

β-oxidation Proper : Mitochondria



Fate of Acetyl CoA: Synthesis of Ketone Bodies





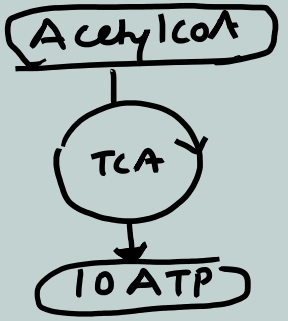
- Cytosol
- Blood glucose = ↓
- Ketone body
  - Acetoacetate
  - Acetone
  - β-Hydroxy Butyrate

Energetics of Beta Oxidation

Palmitoyl CoA + 7 CoASH + 7 FAD + 7 NAD^+ + 7 H_2O → 8 Acetyl CoA + 7 $FADH_2$ + 7 NADH + 7H^+

16C 2C

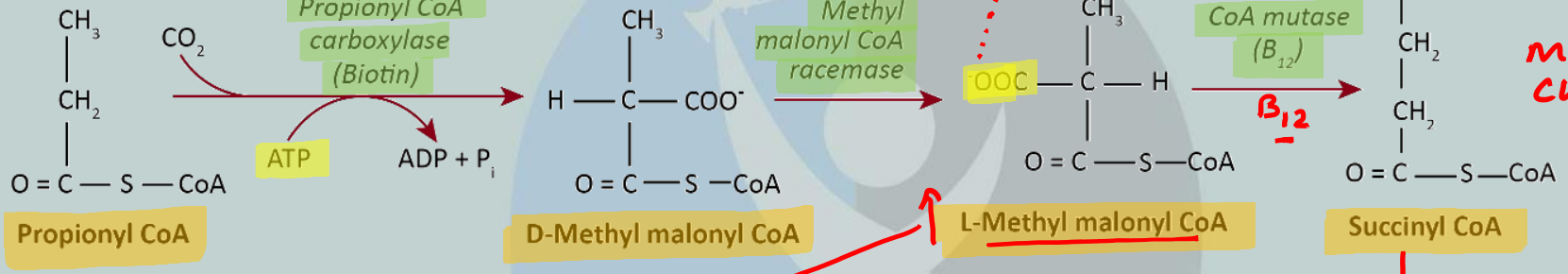
Mechanism	ATP Yield
I. β-Oxidation 7 cycles	
7 $FADH_2$ (Each $FADH_2$ gives 1.5 ATP) 7 × 1.5 =	10.5
7 NADH (Each NADH liberates 2.5 ATP) 7 × 2.5 =	17.5
I. From 8 Acetyl CoA Each acetyl CoA is further oxidized in TCA cyle and provides 10 ATP equivalent energy	80
Total energy from one mole of palmitoyl coA	108
Energy utilized for activation	- 2
Net yield from one molecule of palmitate(16C)	106



Palmitate → Palmityl coA
ATP → AMP

17C → 2C Acetyl CoA (7) + 3C Propionyl CoA (1)

Oxidation of Odd Carbon Chain Fatty Acids



mito chondria

Deficiency of vit B12 → Peripheral Neuropathy

Succinate → Fumarate → Malate

Malate → Malate → OAA (cytosol)

OAA → PEP → F1,6DP → F6P → G-6-P → Glucose (SER)

Biosynthesis of Fatty Acids

Imp

Conditions

- Blood Glucose – High
- Insulin – High
- Citrate – High
- ATP – High
- NADPH – High

Substrate

- Acetyl CoA
- Transport form: Citrate
- Energy: NADPH

Location

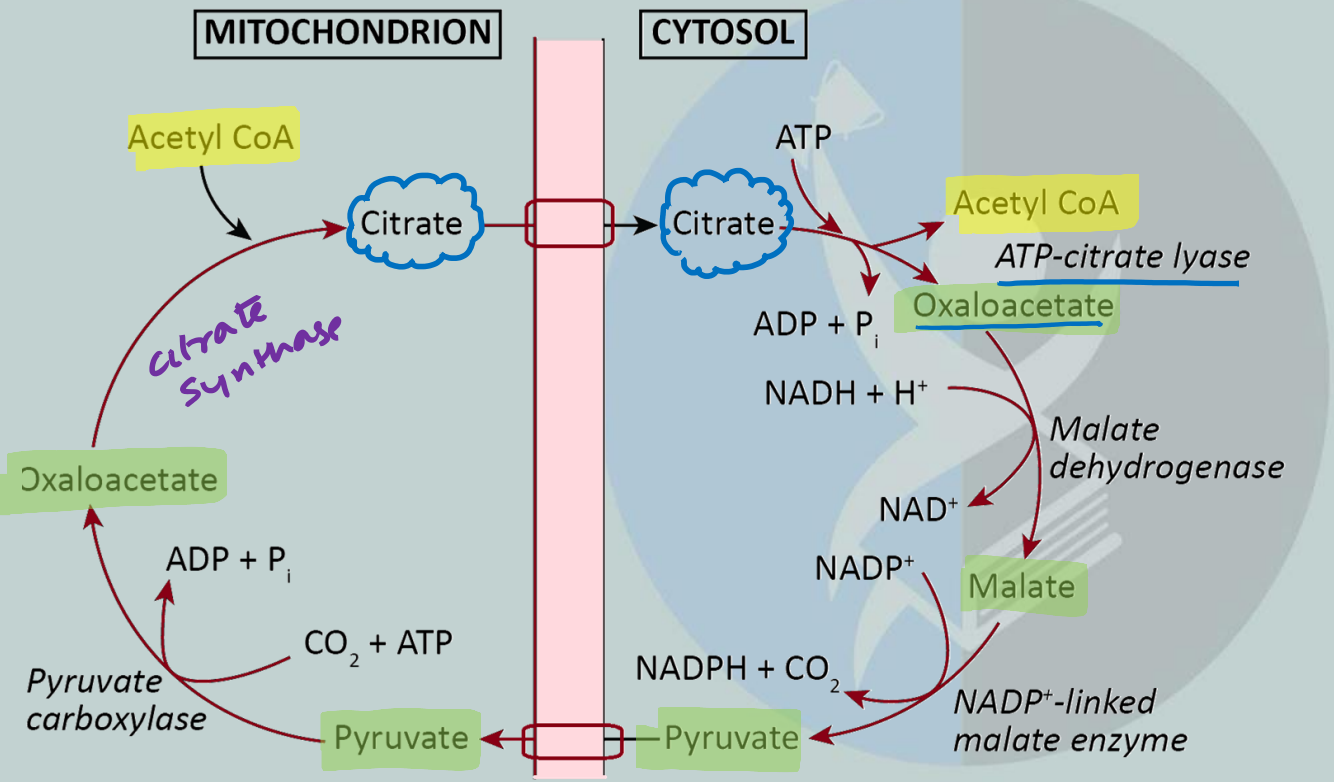
Cytosol of Liver and Adipose Tissues

Regulatory Enzyme

Acetyl CoA Carboxylase ← (+) Citrate, Insulin

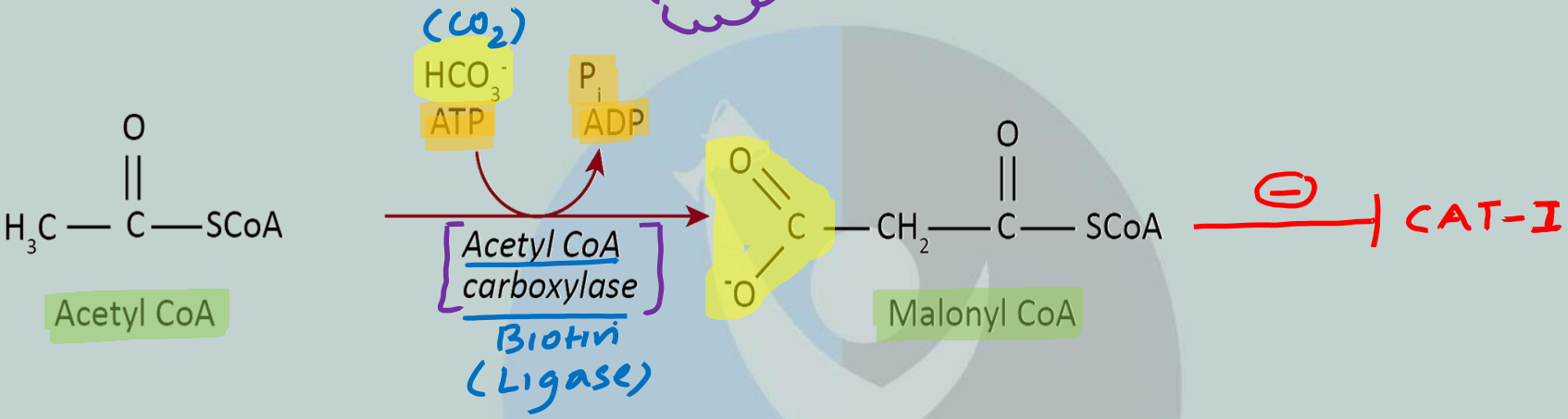
Transport of Acetyl CoA into the Cytosol

Transport form for acetyl CoA from mitochondria to cytosol : citrate



Committed and Regulatory Step

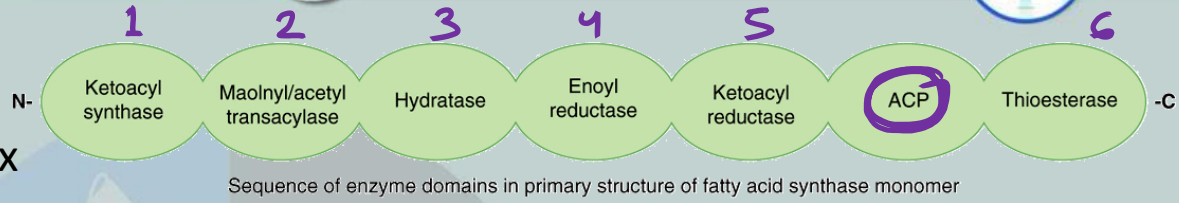
Imp



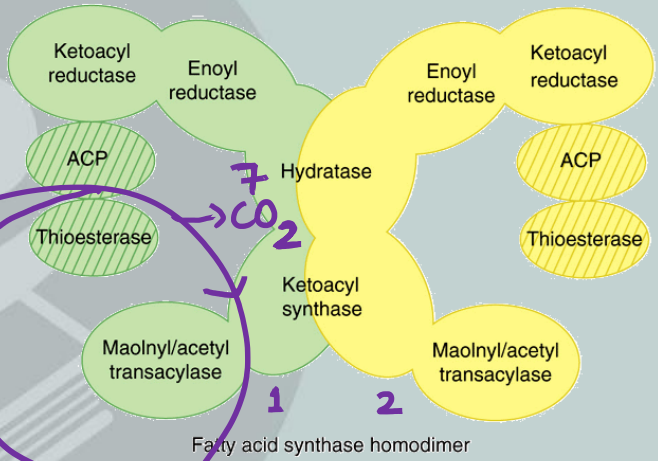
- **Intrinsic Regulation**
  - Activator : citrate
  - Inhibitor : AMP (ADP), Palmitoyl CoA
- **Extrinsic Regulation**
  - Activator : Insulin (dephosphorylation)
  - Inhibitor : Glucagon (Phosphorylation)

Fatty Acid Synthase of Eukaryotes

- Multifunctional enzyme complex
- Dimer
- Each Subunit has 6 different enzyme activity
- Associated Acyl Carrier Protein



Sequence of enzyme domains in primary structure of fatty acid synthase monomer



Fatty acid synthase homodimer

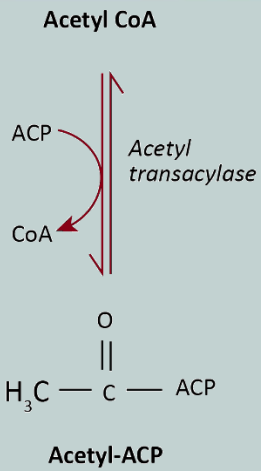
1. Condensation
2. Reduction (NADPH)
3. Dehydration
4. Reduction (NADPH)

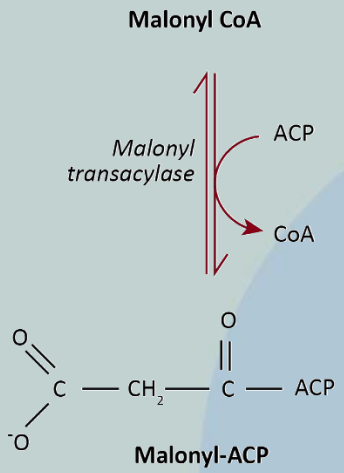
2C
1 acetyl CoA
7 Malonyl CoA
3C

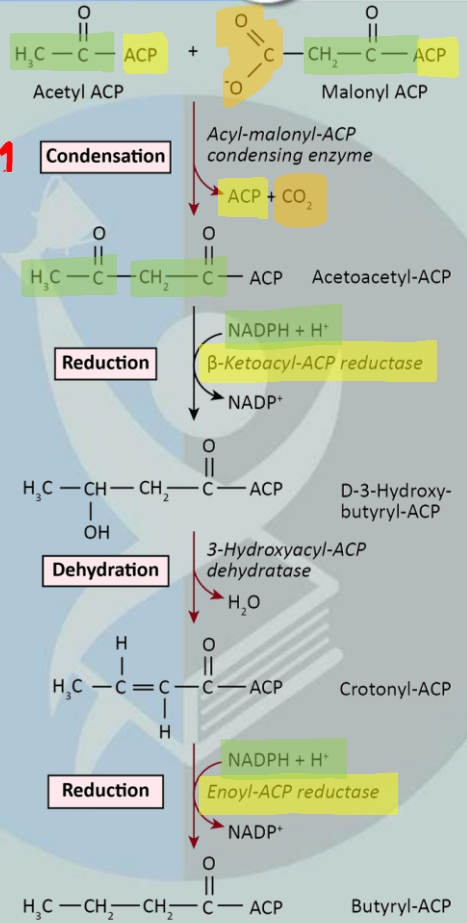
7 → CO_2

(7)

1 Palmitoyl CoA (16C)



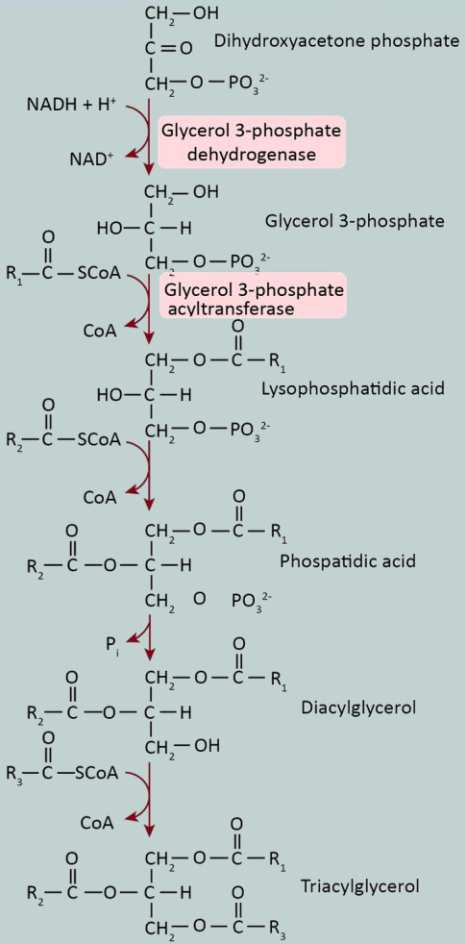




16C Palmitoyl CoA

1 Acetyl CoA
7 Malonyl CoA
14 NADPH

7 acetyl CoA
7 ATP
7 ADP + 1P
7 malonyl CoA



Synthesis of Tri-acyl Glycerol

- Glycerol is derived from DHAP
- Reaction in cytosol.
- Acyl transferase

DHAP → Glycerol-3-P

Acyl CoA → Lyso-phosphatidic acid

Acyl CoA → Phosphatidic acid

DAG

Acyl CoA → TAG

Cholesterol Biosynthesis → Imp

Conditions

- Blood Glucose – High
- Insulin – High
- Acetyl CoA – High
- Citrate – High
- ATP – High
- NADPH – High

Substrate

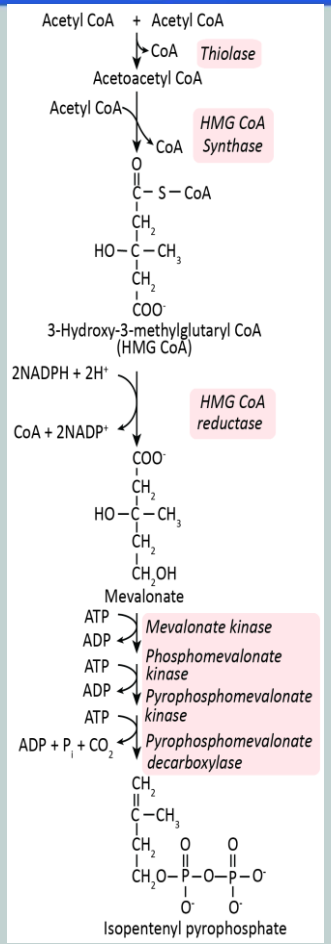
- Acetyl CoA
- Transport form: Citrate
- Energy: NADPH

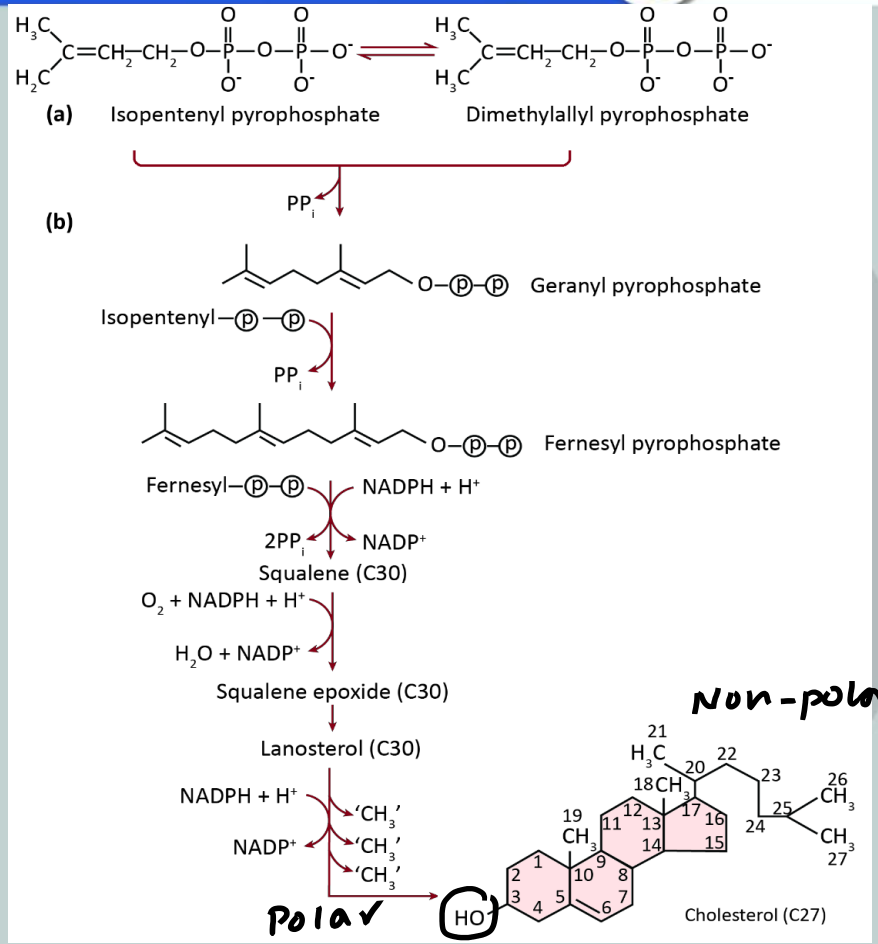
Location

SER of Liver

Regulatory Enzyme

HMG CoA Reductase



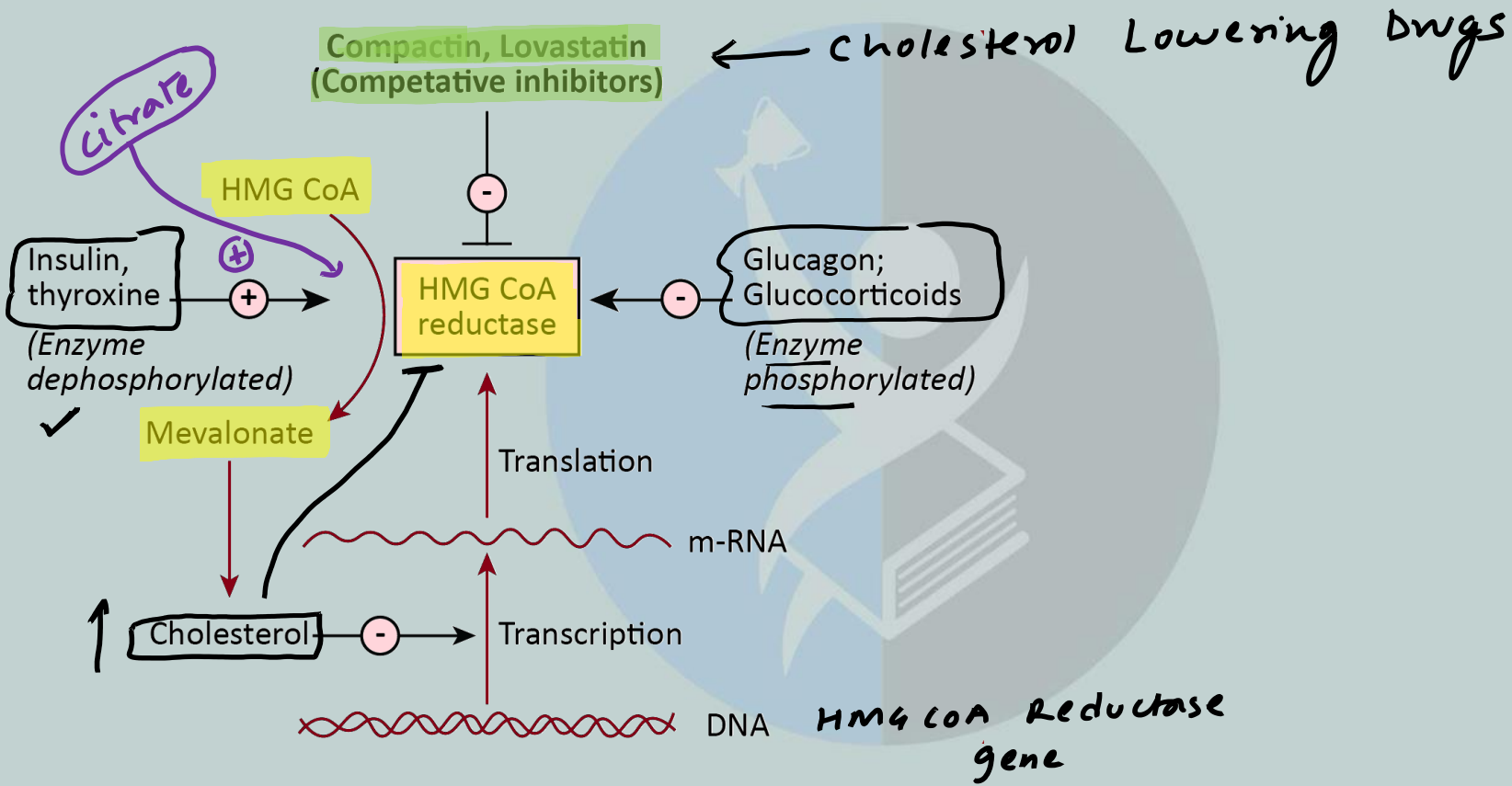


Cytosol

- Mevalonate Pathway
- Regulatory step : HMG CoA Reductase

- Squalene onwards rxn → SER

Regulatory Step in Cholesterol Biosynthesis



AMINO ACID BIOSYTHESIS

Essential, Semi essential and Non-Essential Amino Acids

Essential

Taken from Diet

- Histidine
- Isoleucine
- Leucine
- Lysine
- Methtione
- Phenyl Alanine
- Threonine
- Tryptophan
- Valine

Semi-Essential

- Cysteine
- Tyrosone
- Arginine

Non-Essential

can be synthesized by animals

- Glycine
- Alanine
- Serine
- Aspartate
- Aspargine
- Glutamate
- Glutamine
- Proline

Precursor for Non-Essential Amino Acids

- 3-Phosphoglycerate → Serine, Glycine
- Pyruvate → Alanine
- α-Keto Glutarate → Glutamate, Glutamine, Proline
- Oxaloacetate → Aspartate, Asparagine

Semi-Essential:

- Ornithine → Arginine
- Phenyl Alanine → Tyrosine
- Methionine → Cysteine

Essential Amino Acids: Synthesized by Plants and Microbes

OAA/Aspartate → Lysine, Methionine, and Threonine (KMT)

Pyruvate → Leucine, Isoleucine, and Valine (L-I-V)

- Acetolactate Pathway
- Branched chain aa

Ribose 5 Phosphate → Histidine

PEP and Erythrose 4 Phosphate → Aromatic Amino Acids

Phenylalanine, Tyrosine, and Tryptophan (YTW)

Shikimic acid Pathway

Amino acid catabolism

Purely Ketogenic

Leucine and Lysine : Acetyl-CoA and/or Acetoacetate

Glucogenic and Ketogenic Both (WIFY)

Phenylalanine & Tyrosine: Fumarate and Acetoacetate

Tryptophan: Alanine and Acetoacetate

Isoleucine: Succinyl CoA and Acetyl CoA

Purely Glucogenic

Gly, Ala, Ser, Cys, Thr: Pyruvate

Glu, Gln, Pro, His, Arg: α-Ketoglutarate

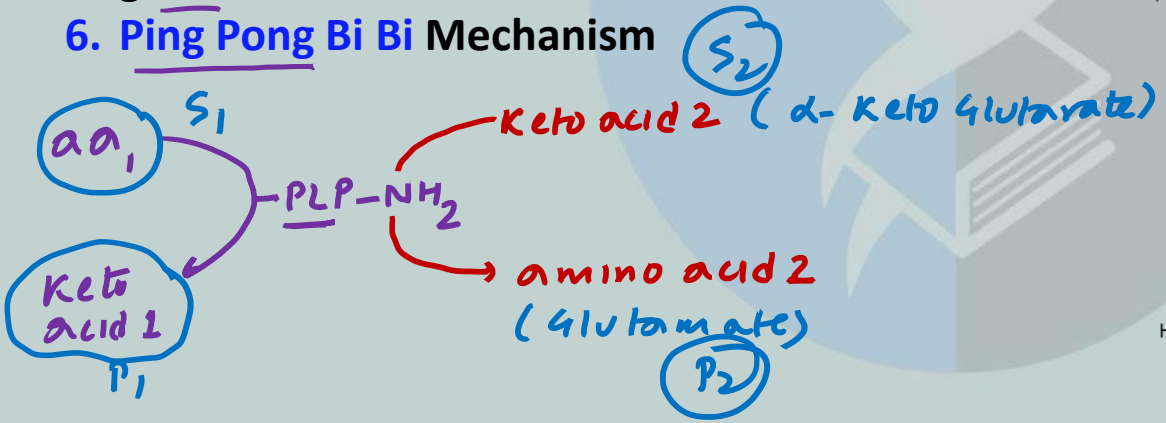
Met, Val, (Thr): Succinyl CoA

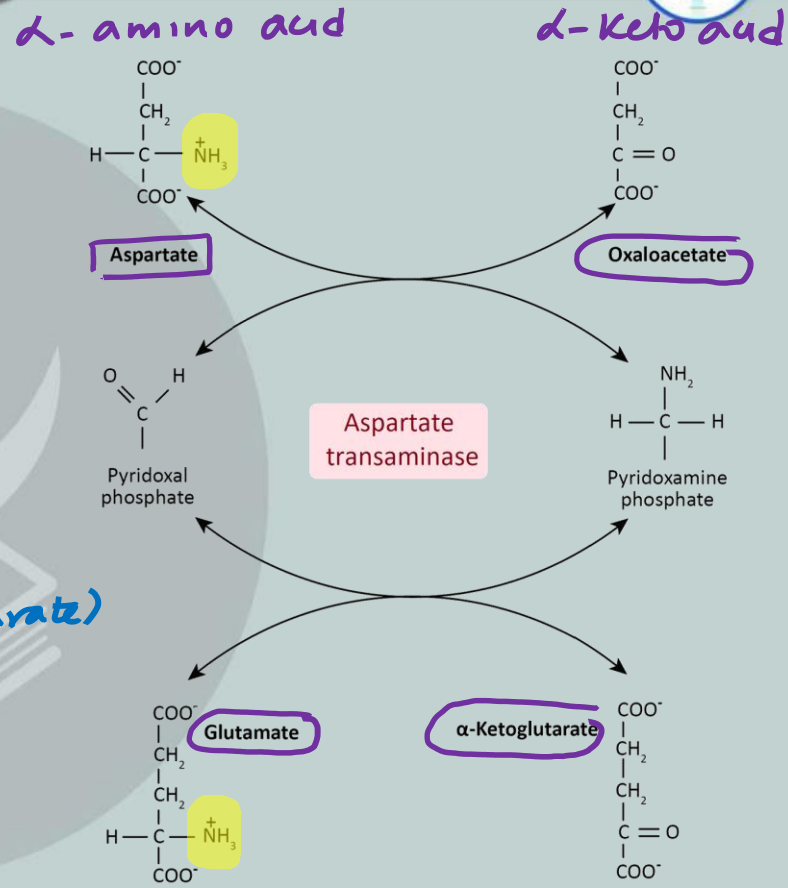
Asp, Asn: OAA

→ → Glucose

Transamination

1. Amino transferase enzyme
2. Requires pyridoxal phosphate (PLP)
3. Reaction is reversible.
4. Production of non-essential amino acids
5. Diverts the excess amino acids towards energy generation.
6. Ping Pong Bi Bi Mechanism





Marker Enzymes

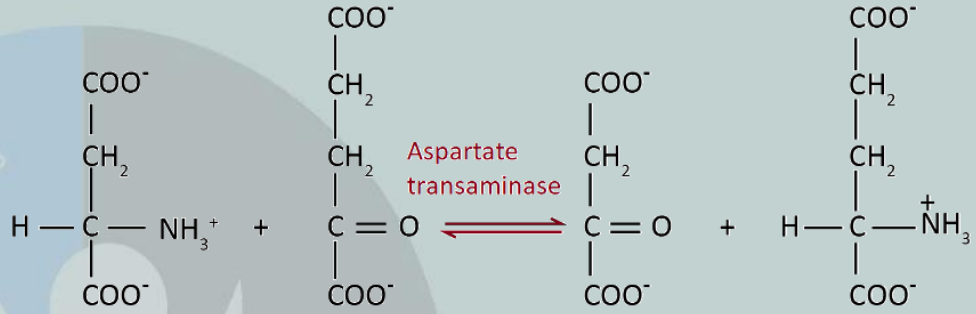
Liver Disorders → Blood (serum) conc^{r} = ↑

Aspartate transaminase (AST): SGOT

Alanine transaminase (ALT): SGPT

- Serum Glutamate - Oxaloacetate transaminase (SGOT)
- Serum Glutamate - Pyruvate transaminase (SGPT)

(a)



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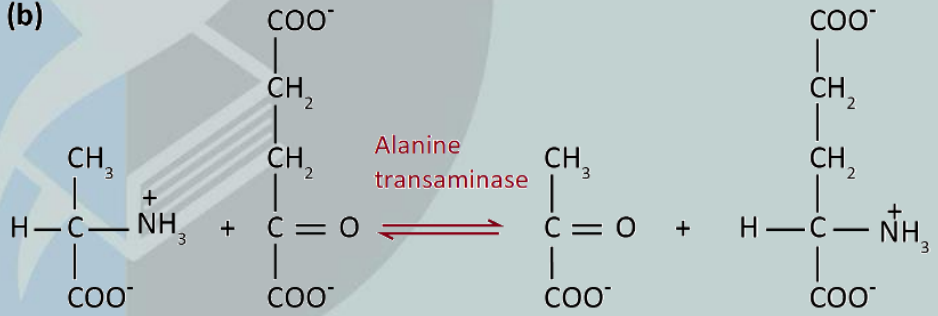
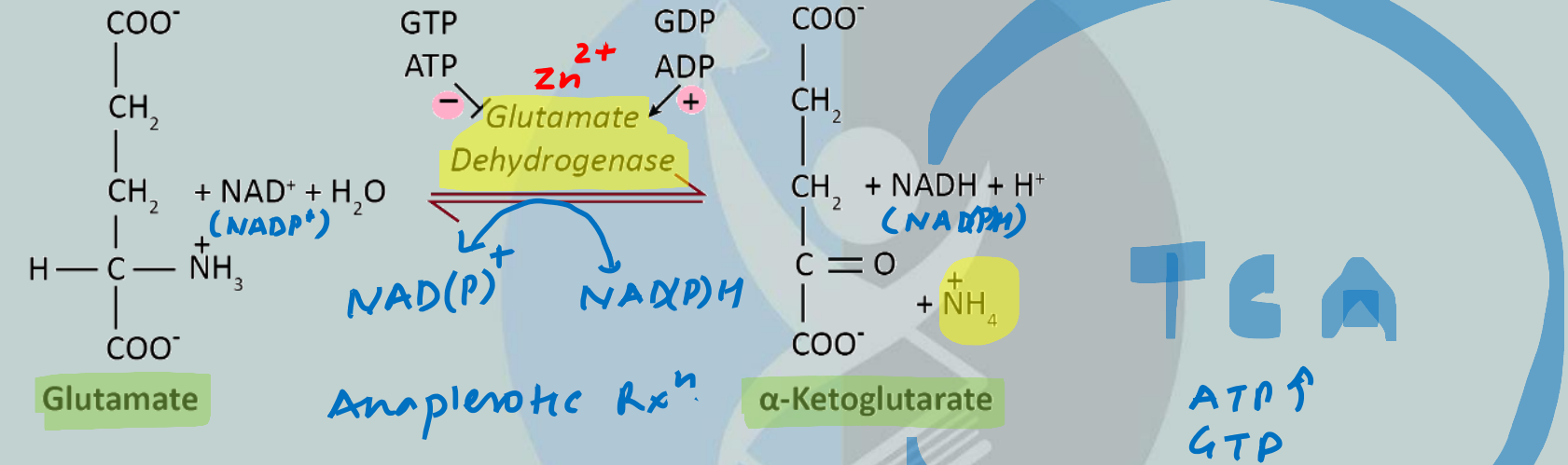


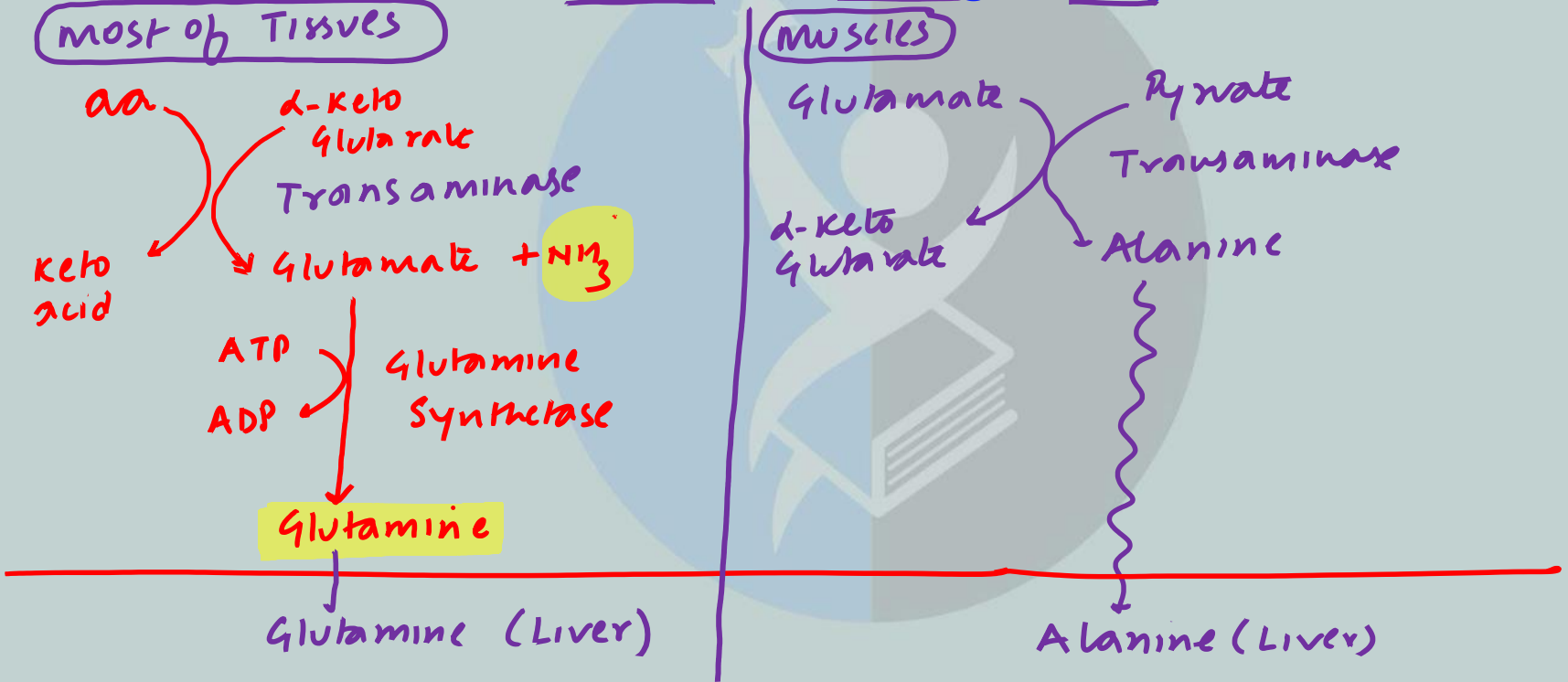
Oxidative deamination of glutamate in Liver Mitochondria



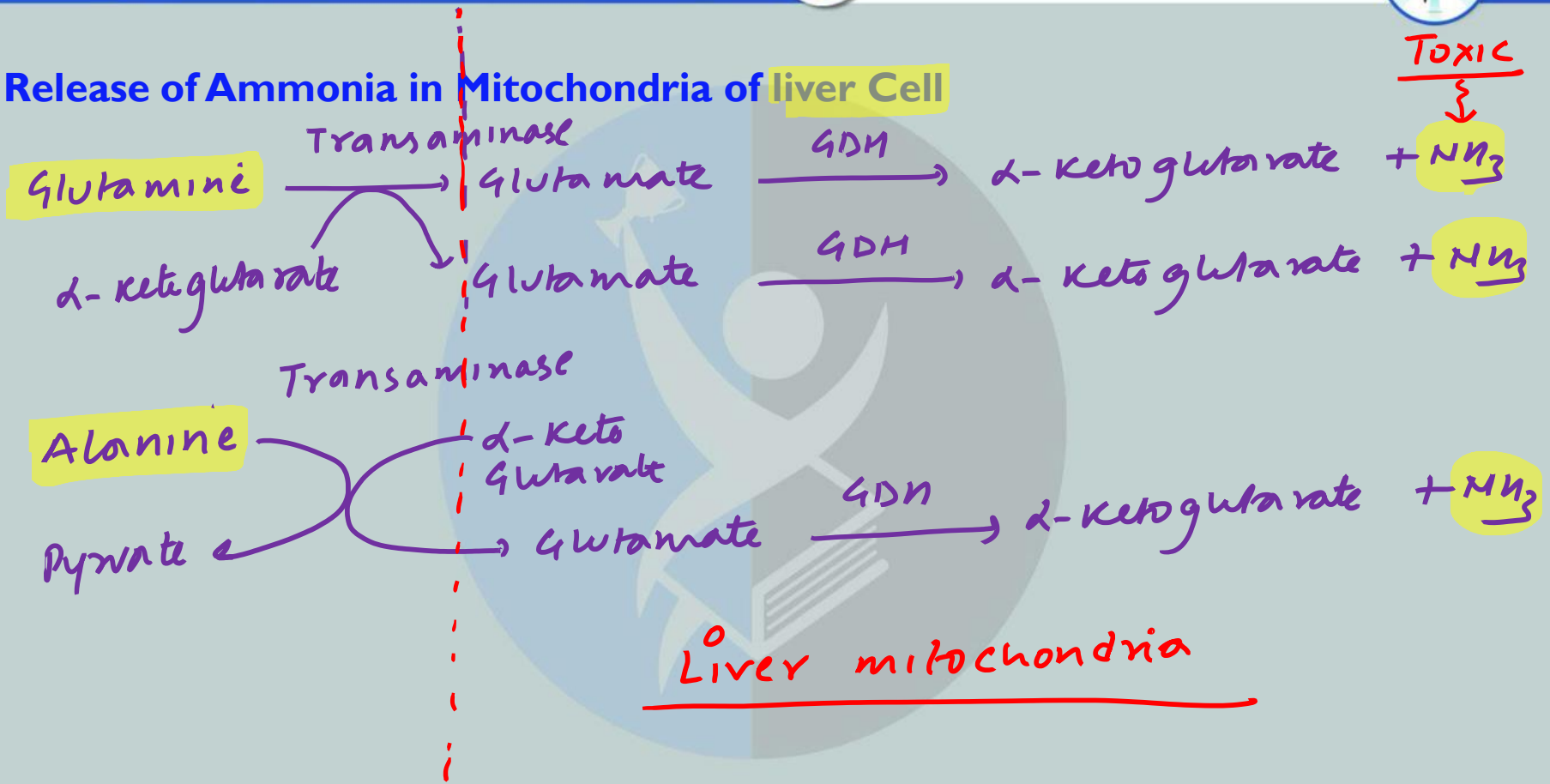
Toxicity of ammonia

METABOLISM OF AMMONIA

1. Glutamine and Alanine: Transport and storage of NH_3



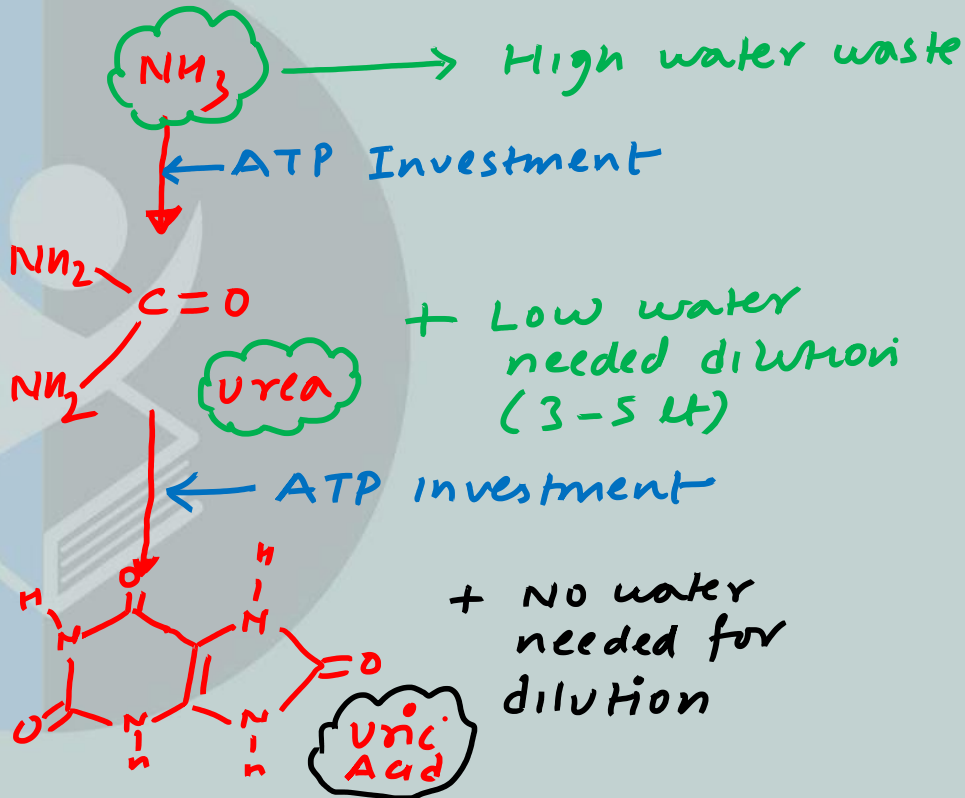
2. Release of Ammonia in Mitochondria of liver Cell



3. Disposal of ammonia:

- **Ammoniotelic:** The aquatic animals dispose off NH_3 into the surrounding water.
- **Ureotelic:** The mammals including man convert NH_3 to urea. Urea is a non-toxic and soluble compound, hence easily excreted.
- **Uricotelic:** Ammonia is converted mostly to uric acid which is least toxic forme.g. reptiles and birds.

Insects

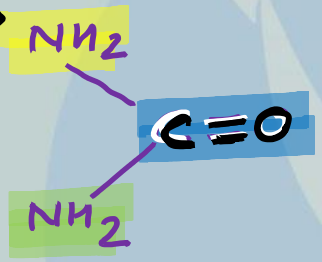


4. UREA CYCLE:

Site: Liver (Mitochondria and Cytosol)

Precursor:

- Ammonia
- Aspartate
- CO_2

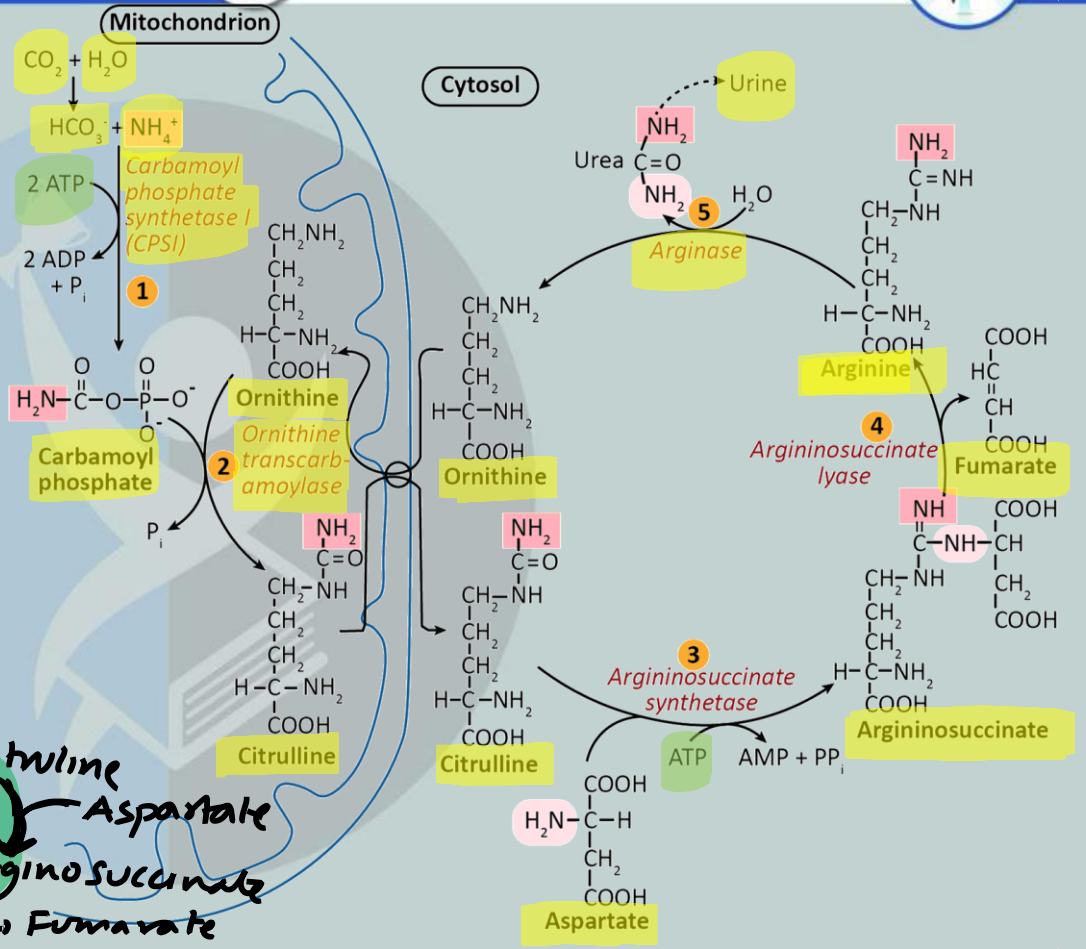


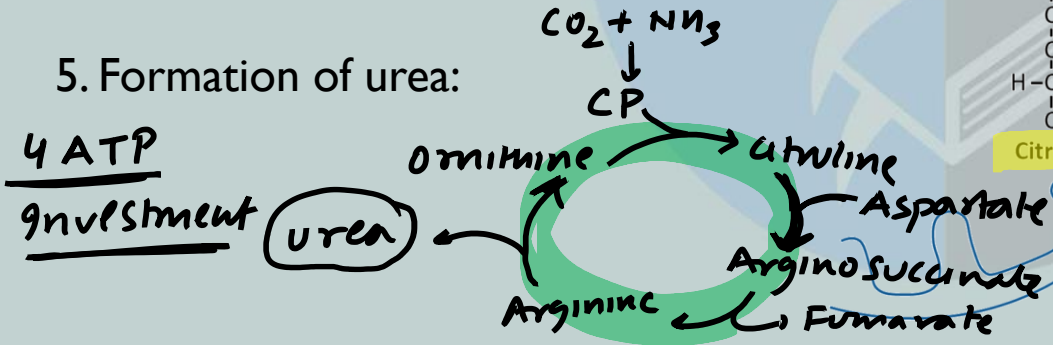
Regulatory Step:

Carbomyl Phosphate Synthetase I ← (+) N-Acetyl Glutamate (NAG)

Steps

1. Synthesis of carbamoyl phosphate
2. Formation of citrulline:
3. Synthesis of arginosuccinate:
4. Cleavage of arginosuccinate:
5. Formation of urea:





Inborn errors of metabolism (Genetic Disorders — Autosomal Recessive)

Enzyme non-functional due to gene mutation.

- **Phenylketonuria:** Phenylalanine hydroxylase
- **Maple Syrup Urine Disease:** Branched-chain alpha-keto acid dehydrogenase complex
- **Alkaptonuria:** Homogentisate oxidase
- **Tyrosinemia Type I:** fumarylacetoacetate hydrolase.
- **Homocystinuria:** Cystathionine beta-synthase

Nucleotide Anabolism (Synthesis)

→ Cytosol
→ Actively dividing cells.

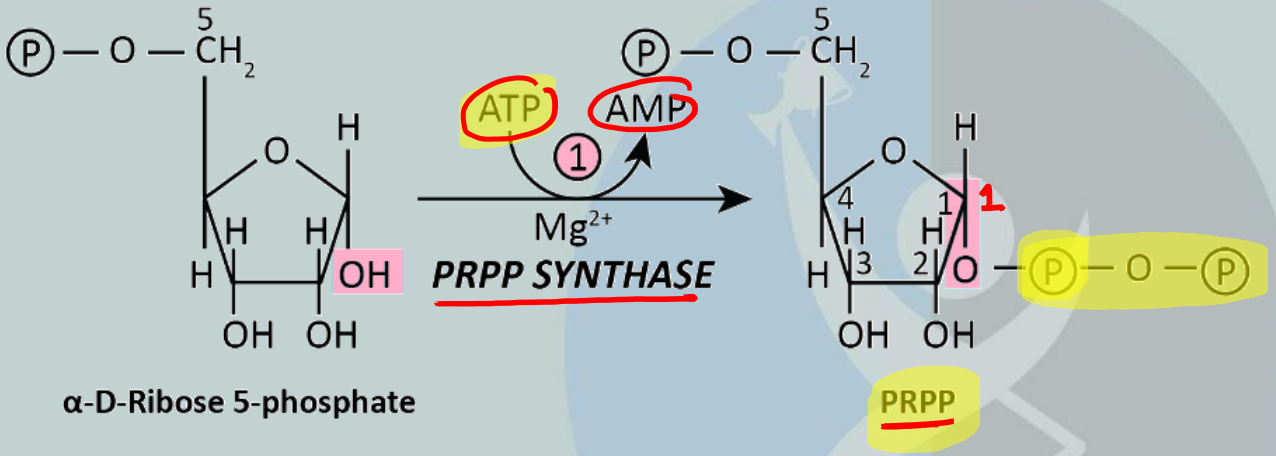
De novo Pathway:

- Actively dividing cells
- Compete new synthesis of base and nucleotide

Salvage Pathway

- Non-dividing cells
- Recycling pathway

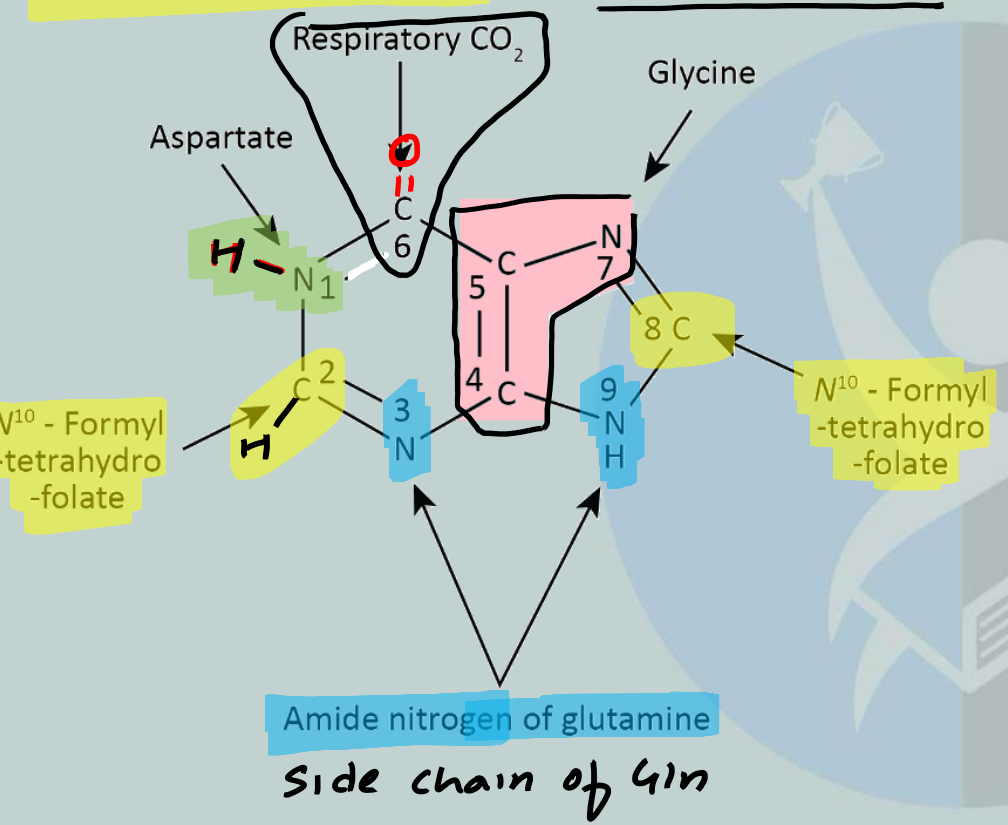
PRPP : Common Requirement for Denovo and Salvage Pathway



5-Phospho
Ribosyl
1-Pyrophosphate
(PRPP)

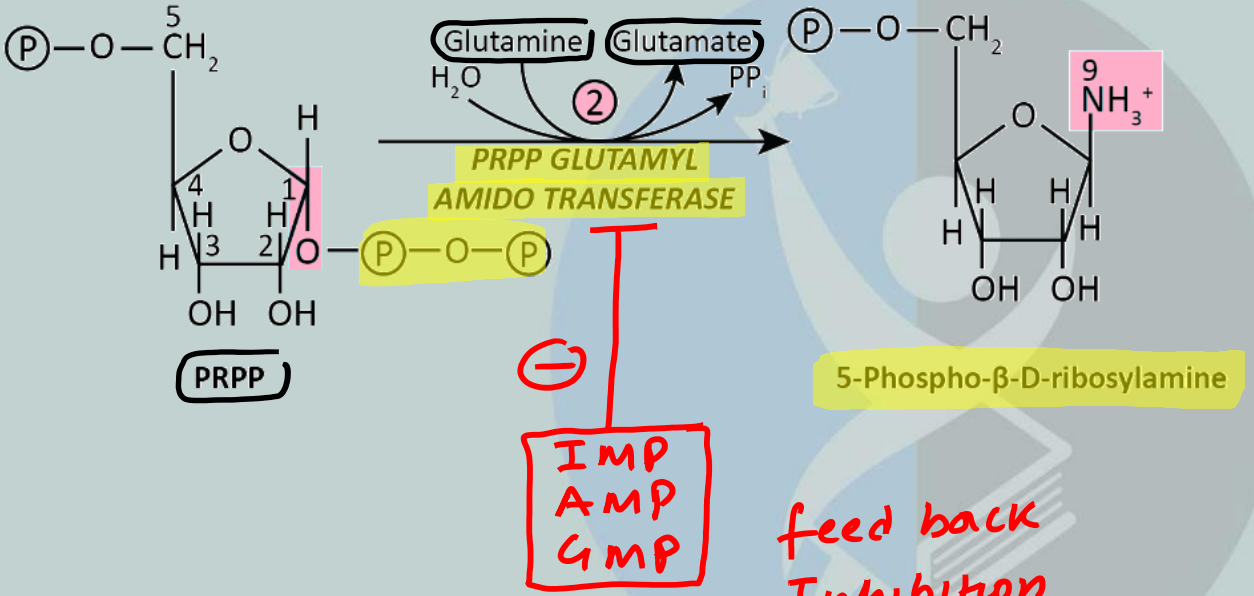
DE NOVO PATHWAY OF PURINE NUCLEOTIDES

Parent Purine = Hypoxanthine
Parent nucleotide = IMP



1. N_1 of purine is derived from amino group of aspartate.
2. C_2 and C_8 arise from formate of N^{10}-formyl Tetra Hydro Folate (THF).
3. N_3 and N_9 are obtained from amide group of glutamine.
4. C_4, C_5 and N_7 are contributed by glycine.
5. C_6 directly comes from CO_2

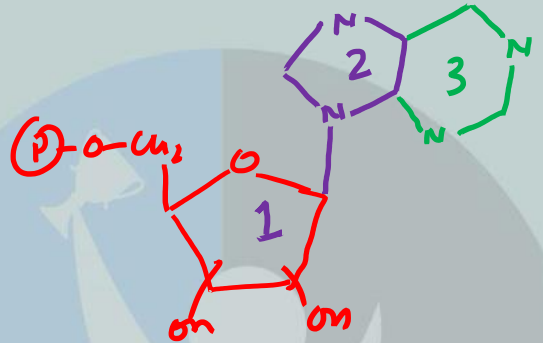
Committed and regulatory step

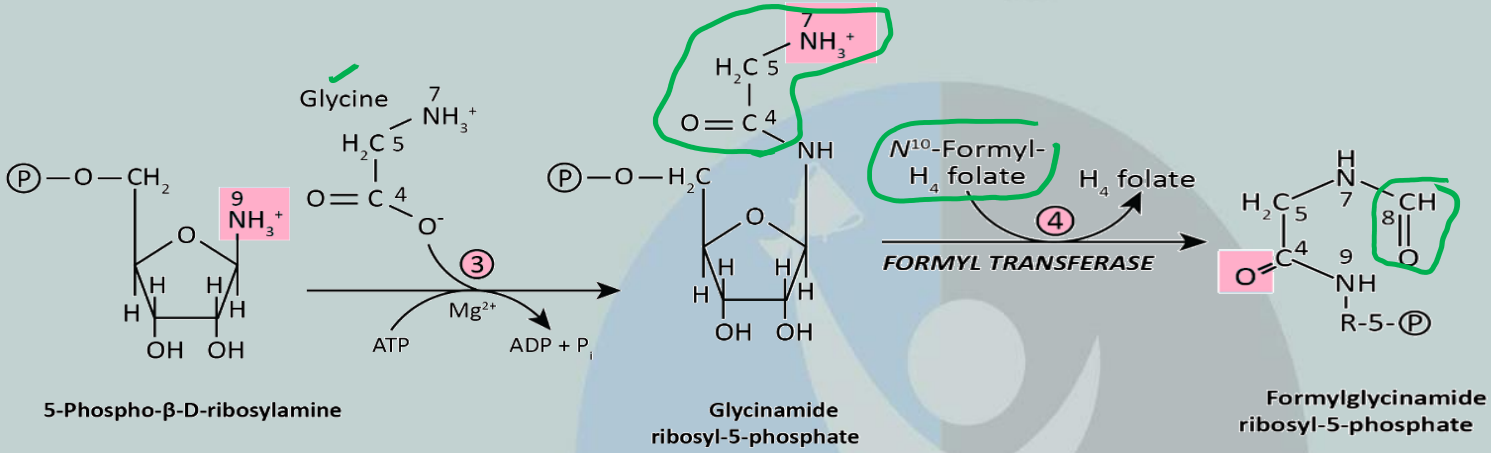


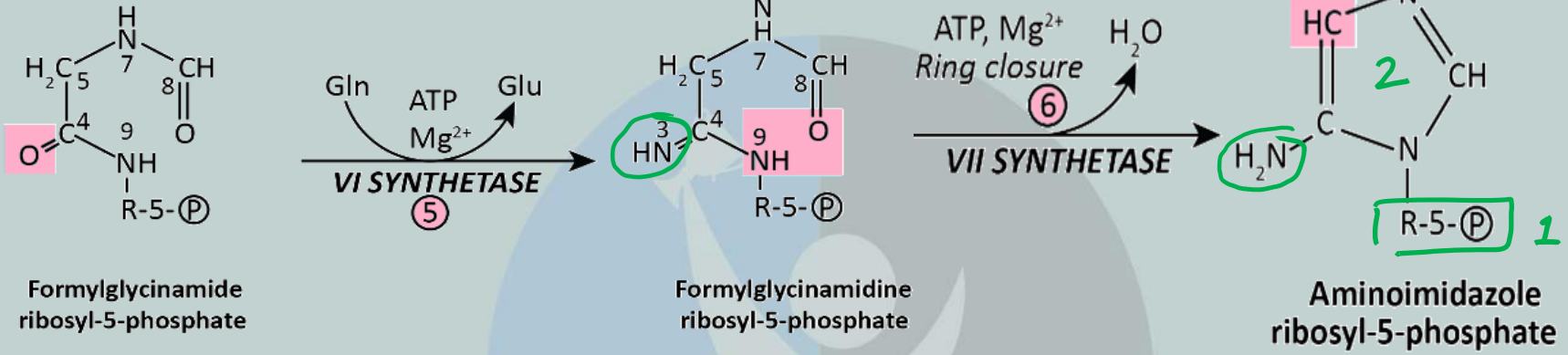
Inhibition: IMP, AMP and GMP

Series of Events:

1. Pentose Phosphate Sugar
2. Imidazole Ring
3. Pyrimidine Ring



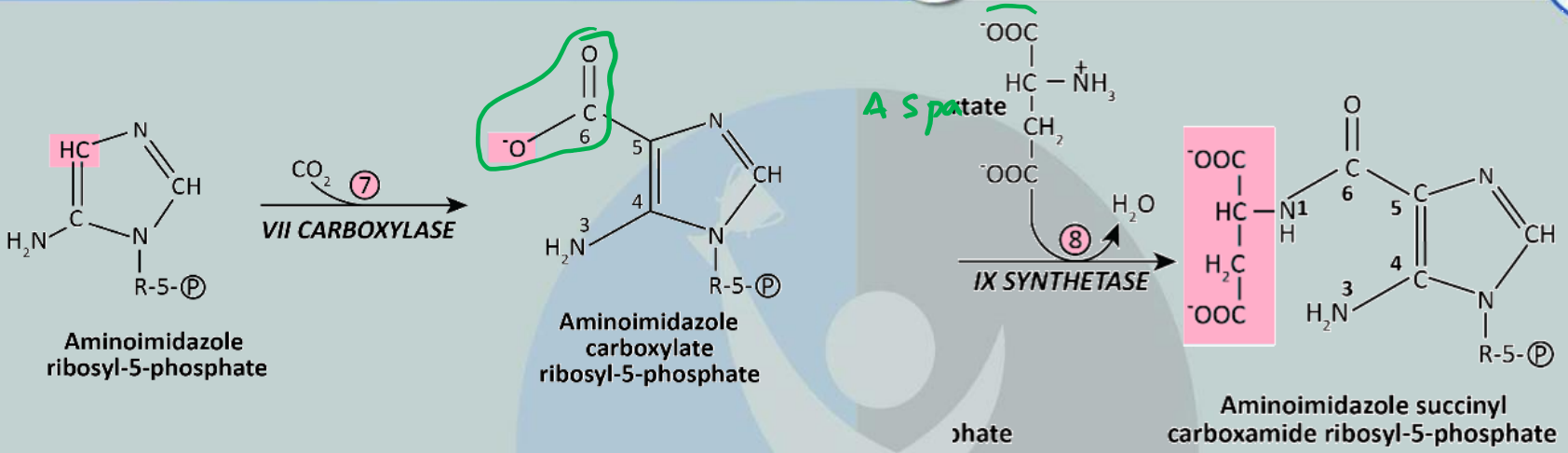

Glycine
ATP
ADP + P$_i$
Mg^{2+}
3
4
FORMYL TRANSFERASE
N^{10}-Formyl-H$_4$ folate
H$_4$ folate
5-Phospho-β-D-ribosylamine
Glycinamide ribosyl-5-phosphate
Formylglycinamide ribosyl-5-phosphate



Formylglycinamide ribosyl-5-phosphate

Formylglycinamidine ribosyl-5-phosphate

Aminoimidazole ribosyl-5-phosphate

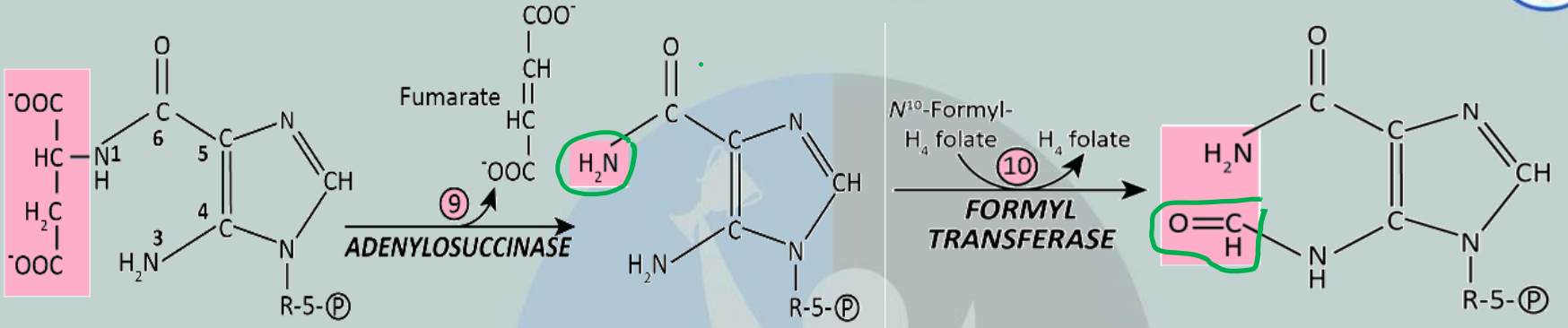


Aminoimidazole ribosyl-5-phosphate

Aminoimidazole carboxylate ribosyl-5-phosphate

phate

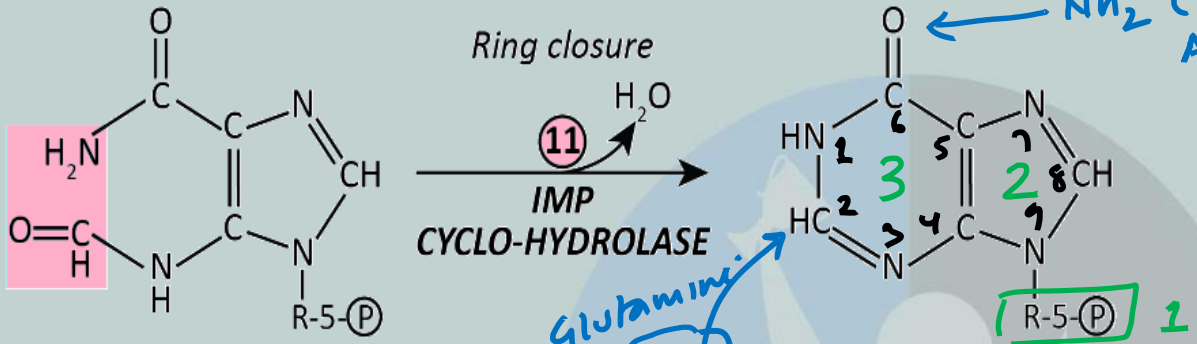
Aminoimidazole succinyl carboxamide ribosyl-5-phosphate



Aminoimidazole succinyl carboxamide ribosyl-5-phosphate

Aminoimidazole carboxamide ribosyl-5-phosphate

(XI) Formimidoimidazole carboxamide ribosyl-5-phosphate

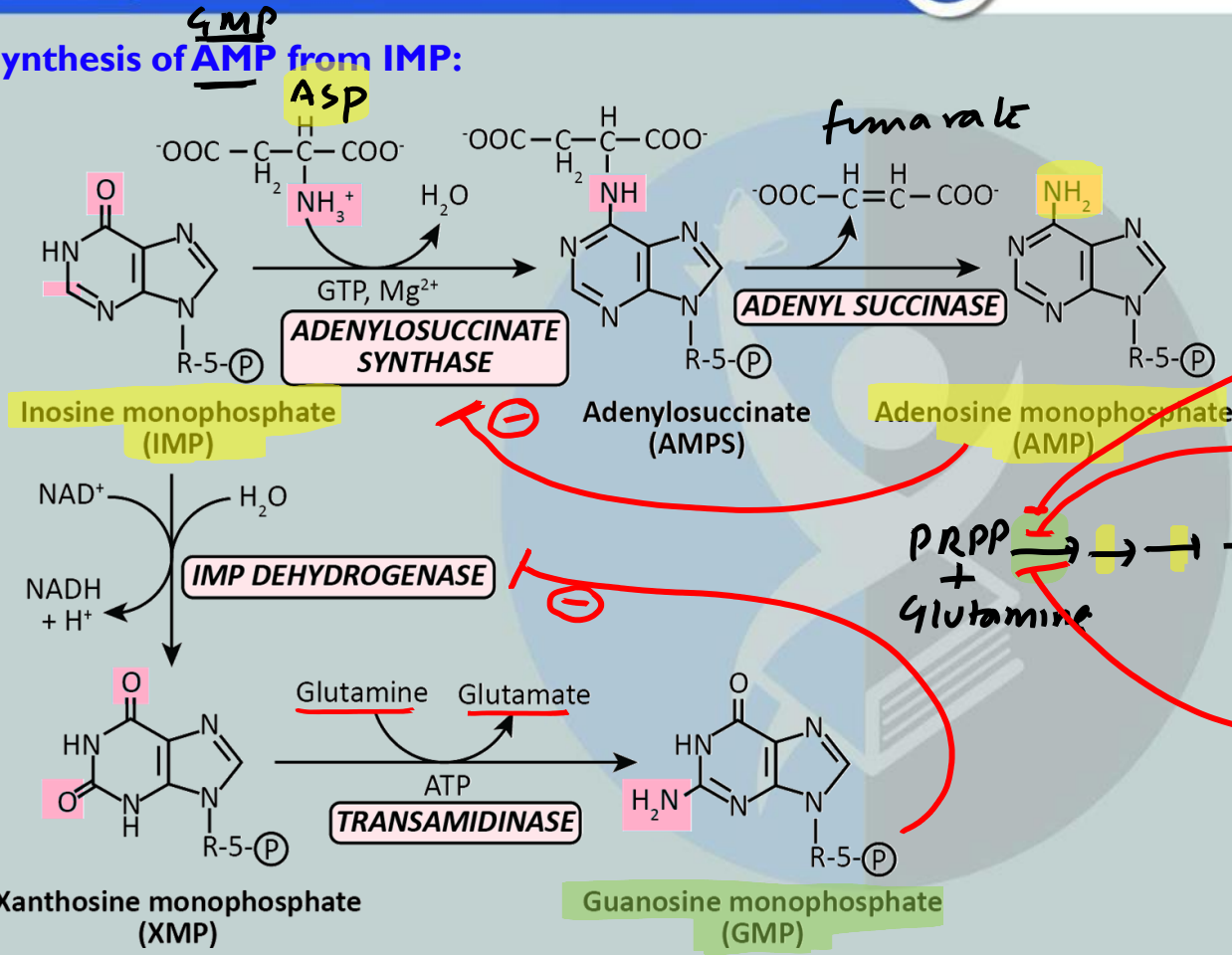


PRPP → 5-Phosphoribosyl Amine → → → → → → → IMP → AMP, GMP

Glutamine → Glutamate

PRPP – Glutamyl Amido transferase.

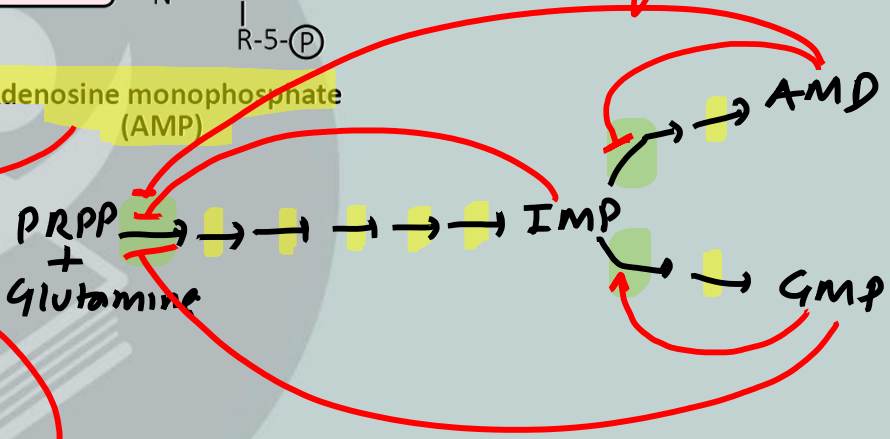
Synthesis of AMP from IMP:



Amino Group

AMP : Aspartate

GMP : Side chain of Glutamine



Inhibitors of Denovo-purine synthesis → Anti-cancer drugs

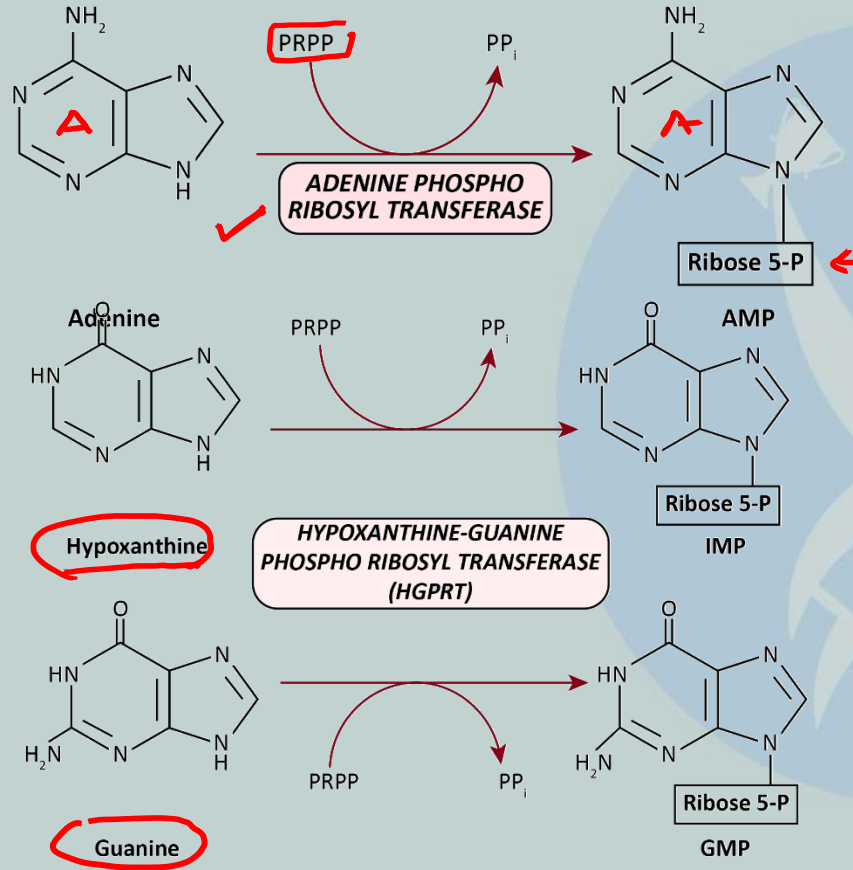
- **Methotrexate, Aminopterin** ⊖ DHF Reductase
- **Azaserine** is an antagonist of glutamine

folic acid → DHF Reductase → THF

THF → N^{10}-formyl THF → Purine (A, G)

THF → N^5 N^{10} methyl THF → Thymine (T)

Salvage pathway for Purines



Adenine + PRPP
↓ APRT
AMP + PPi

PRPP

Hx + PRPP → IMP + PPi

HGPRT

G + PRPP → GMP + PPi

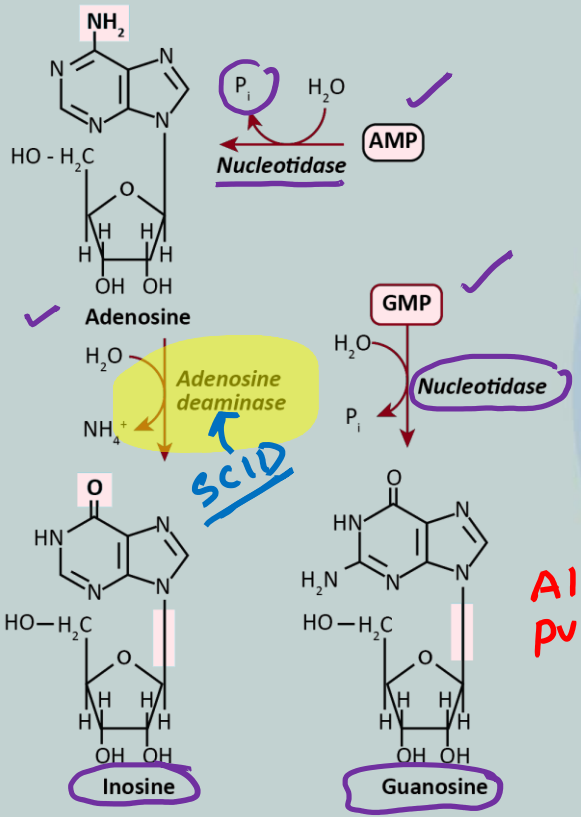
gene on → X-linked

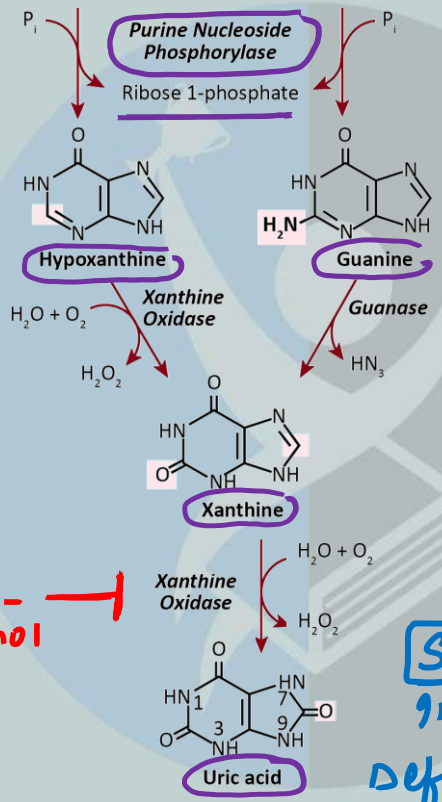
Deficiency : Lesch Nyan-Syndrome

DEGRADATION OF PURINE NUCLEOTIDES

Inosine

Guanosine ← Nucleosides





End Product of Purine catabolism

[uric acid] ↑

Disorder : Gout

Treatment → Allopurinol

inhibitor of xanthine oxidase

SCID : Severe combined immunodeficiency (B=↓ T=↓)

Deficiency of Adenosine deaminase

DISORDERS OF PURINE CATABOLISM

Adenosine deaminase (ADA) deficiency causes **severe combined immunodeficiency (SCID)**

Excess catabolism of Purine: Hyperuricemia and gout

- uric acid ↑

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